LOTRONEX® and its authorized generic alosetron hydrochloride:

Understanding the Benefits and Risks

The LOTRONEX REMS Program™ Prescriber Education Slide Deck

 LOT15049 08/15

Please see complete Prescribing Information for LOTRONEX®/alosetron hydrochloride.

Table of Contents

Important

Modified LOTRONEX REMS Program™

The modified LOTRONEX REMS Program™ has replaced the previous Prescribing Program for LOTRONEX™

❶ Prescribers are no longer required to affix prescribing program stickers to written prescriptions for LOTRONEX®/alosetron hydrochloride.

❷ Pharmacies are no longer required to only dispense LOTRONEX®/alosetron hydrochloride for a paper prescription with an affixed prescribing program sticker. **Electronic prescriptions are now allowed.**

❸ Patients are no longer required to complete and submit a Patient Acknowledgement Form. Instead, a Patient Education Sheet is available for the prescriber to discuss with the patient.

Section 1:

Purpose

Please see complete Prescribing Information for LOTRONEX®/alosetron hydrochloride for full details about risks.

Purpose

By reviewing the information provided in this presentation, Health Care Providers who prescribe LOTRONEX®/alosetron hydrochloride will better understand the:

- **Risks and benefits of LOTRONEX®/alosetron hydrochloride;**
- **Etiology of irritable bowel syndrome (IBS);**
- **LOTRONEX REMS Program™.**

What is a REMS?

A REMS (Risk Evaluation and Mitigation Strategy) is a program required by the FDA to manage known or potential serious risks associated with a drug product. FDA has determined that a REMS is necessary to ensure that the benefits of LOTRONEX and its authorized generic alosetron hydrochloride tablets outweigh serious gastrointestinal adverse reactions in patients.

Goals and Objectives

The LOTRONEX REMS Program™ was implemented to help reduce the risks of serious gastro-intestinal (GI) adverse events.

The goals and objectives of the LOTRONEX REMS Program™ are to mitigate the risks of ischemic colitis (IC) and serious complications of constipation (CoC) associated with LOTRONEX®/alosetron hydrochloride by:

- **Informing prescribers of LOTRONEX®/alosetron hydrochloride about:**
  - **the serious risks of IC and serious CoC associated with LOTRONEX®/alosetron hydrochloride**
  - **the importance of understanding that LOTRONEX®/alosetron hydrochloride should only be used in severely affected diarrhea-predominant irritable bowel syndrome patients for whom the benefits exceed the risks**
  - **the importance of counseling patients about the risks of IC and serious CoC**
- **Informing patients about the risks of IC and CoC and actions to take should they experience early warning signs and symptoms of these risks.**

Section 2:

Indication and Usage

Please see complete Prescribing Information for LOTRONEX®/alosetron hydrochloride for full details about risks.

Indication and Usage

- LOTRONEX®/alosetron hydrochloride is indicated ONLY for women with severe diarrhea-predominant IBS who have:
  - ✓ **chronic IBS symptoms (generally lasting 6 months or longer),**
  - ✓ **had anatomic or biochemical abnormalities of the GI tract excluded, and**
  - ✓ **not responded adequately to conventional therapy.**
- Diarrhea-predominant IBS is severe if it includes diarrhea and one or more of the following:
  - ✓ **frequent and severe abdominal pain/discomfort,**
  - ✓ **frequent bowel urgency or fecal incontinence,**
  - ✓ **disability or restriction of daily activities due to IBS.**
- Because of infrequent but serious GI adverse reactions associated with alosetron hydrochloride, the indication is restricted to those patients for whom the benefit-to-risk balance is most favorable.
- Clinical studies have not been performed to adequately confirm the benefits of alosetron hydrochloride in men.

Section 3:

Important Safety Information

Please see complete Prescribing Information for LOTRONEX®/alosetron hydrochloride for full details about risks.

Boxed Warning

WARNING: SERIOUS GASTROINTESTINAL ADVERSE REACTIONS

Infrequent but serious gastrointestinal adverse reactions have been reported with the use of alosetron hydrochloride. These events, including ischemic colitis and serious complications of constipation, have resulted in hospitalization, and rarely, blood transfusion, surgery, and death.

Please see complete Prescribing Information for LOTRONEX®/alosetron hydrochloride for full details about risks.

Boxed Warning (cont'd)

- Alosetron hydrochloride is indicated only for women with severe diarrhea-predominant irritable bowel syndrome (IBS) who have not responded adequately to conventional therapy.
- Alosetron hydrochloride should be discontinued immediately in patients who develop constipation or symptoms of ischemic colitis. Patients should immediately report constipation or symptoms of ischemic colitis to their prescriber. Alosetron hydrochloride should not be resumed in patients who develop ischemic colitis. Patients who have constipation should immediately contact their prescriber if the constipation does not resolve after alosetron hydrochloride is discontinued. Patients with resolved constipation should resume alosetron hydrochloride only on the advice of their treating prescriber.

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Warnings and Precautions

Serious Complications of Constipation

- Some patients have experienced serious complications of constipation without warning. Examples include:
  - ✓ **obstruction, ileus, impaction, toxic megacolon, and secondary bowel ischemia have been reported with use of alosetron hydrochloride during clinical trials**
  - ✓ **in addition, rare cases of intestinal perforation and death have been reported from post-marketing clinical practice**
  - ✓ **in some cases, complications of constipation required intestinal surgery, including colectomy**
- The incidence of serious complications of constipation was ~0.1%, or 1 per 1,000 patients, in women receiving either alosetron hydrochloride or placebo.
- Patients who are elderly, debilitated, or taking additional medications that decrease GI motility may be at greater risk for complications of constipation.
- Alosetron hydrochloride should be discontinued immediately in patients who develop constipation.

Please see complete Prescribing Information for LOTRONEX®/alosetron hydrochloride for full details about risks.

Warnings and Precautions (cont'd)

Ischemic Colitis

- Some patients have experienced symptoms of ischemic colitis without warning.
- Ischemic colitis has been reported in patients receiving alosetron hydrochloride in clinical trials as well as during marketed use of the drug.
- In IBS clinical trials:
  - ✓ **cumulative incidence of ischemic colitis in women receiving alosetron hydrochloride was:**
    - **0.2%, or 2 per 1,000 patients (95% CI 1 to 3), over 3 months**
    - **0.3%, or 3 per 1,000 patients (95% CI 1 to 4), over 6 months**
  - ✓ **patient experience in controlled clinical trials is insufficient to estimate the incidence of ischemic colitis in patients taking alosetron hydrochloride for longer than 6 months**

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Warnings and Precautions (cont'd)

Ischemic Colitis

- Alosetron hydrochloride should be discontinued immediately in patients with signs of ischemic colitis, e.g., rectal bleeding, bloody diarrhea, or new or worsening abdominal pain.
- Because ischemic colitis can be life threatening, patients with signs or symptoms of ischemic colitis should be evaluated promptly and have appropriate diagnostic testing performed.
- Treatment with alosetron hydrochloride should not be resumed in patients who develop ischemic colitis.

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Contraindications

- Alosetron hydrochloride should not be initiated in patients with constipation.
- Alosetron hydrochloride is contraindicated in patients with a history of:
  - ✓ **chronic or severe constipation or sequelae from constipation;**
  - ✓ **intestinal obstruction, stricture, toxic megacolon, gastrointestinal perforation, and/or adhesions;**
  - ✓ **ischemic colitis, impaired intestinal circulation, thrombophlebitis, or hypercoagulable state;**
  - ✓ **Crohn's disease or ulcerative colitis;**
  - ✓ **diverticulitis;**
  - ✓ **severe hepatic impairment.**
- Concomitant administration of alosetron hydrochloride and fluvoxamine is contraindicated.

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Drug Interactions

- In vivo data suggest that alosetron hydrochloride is primarily metabolized by cytochrome P450 (CYP) 1A2, with minor contributions from CYP3A4 and CYP2C9. Therefore, inducers or inhibitors of these enzymes may change the clearance of alosetron hydrochloride.
- Concomitant administration of alosetron hydrochloride and fluvoxamine is contraindicated.
- Concomitant administration of alosetron hydrochloride and moderate CYP1A2 inhibitors, including quinolone antibiotics and cimetidine, has not been evaluated, but should be avoided unless clinically necessary because of similar potential drug interactions.

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Drug Interactions (cont'd)

- Caution should be used when alosetron hydrochloride and ketoconazole are administered concomitantly.
- Coadministration of alosetron hydrochloride and strong CYP3A4 inhibitors, such as clarithromycin, telithromycin, protease inhibitors, voriconazole, and itraconazole has not been evaluated but should be undertaken with caution because of similar potential drug interactions.
- The effect of induction or inhibition of other pathways on exposure to alosetron hydrochloride and its metabolites is not known.

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Use in Specific Populations

- Pregnancy Category B.
- It is not known whether alosetron hydrochloride is excreted in human milk; caution should be exercised when alosetron hydrochloride is administered to a nursing woman.
- Safety and effectiveness in pediatric patients have not been established.
- Post-marketing experience suggests that elderly patients may be at greater risk for complications of constipation; therefore, appropriate caution and follow-up should be exercised if alosetron hydrochloride is prescribed for these patients.
- Increased exposure to alosetron hydrochloride and/or its metabolites is likely to occur in patients with hepatic impairment. Alosetron hydrochloride should not be used in patients with severe hepatic impairment and should be used with caution in patients with mild or moderate hepatic impairment.

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Adverse Reactions Reported in ≥ 1% of IBS Patients[a]

Gastrointestinal Adverse Reactions	Alosetron hydrochloride 1 mg BID (n=8,328[b])	**Placebo** (n=2,363)
Constipation[c]	29%	6%
Abdominal discomfort and pain	7%	4%
Nausea	6%	5%
GI discomfort and pain	5%	3%
Abdominal distention	2%	1%
Regurgitation and reflux	2%	2%
Hemorrhoids	2%	1%

[a] Reported in ≥1% of alosetron hydrochloride patients and occurring more frequently on alosetron hydrochloride 1 mg twice-a-day than on placebo.

[b] Data reported from 22 repeat-dose studies in patients with IBS treated for 8 to 24 weeks.

[c] $P<0.0001$ vs placebo.

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Adverse Reactions

- Constipation is a frequent and dose-related side effect of treatment with alosetron hydrochloride.
- In clinical studies constipation was reported in ~29% of patients with IBS treated with alosetron hydrochloride 1 mg twice daily (n=9,316).
  - ✓ **The effect was statistically significant compared with placebo (*P*<0.0001);**
  - ✓ **11% of patients treated with alosetron hydrochloride 1 mg twice daily withdrew from the studies due to constipation.**
- Although the number of IBS patients treated with alosetron hydrochloride 0.5 mg twice daily is relatively small (n 243), 11% of patients reported constipation and 4% of patients withdrew from clinical studies due to constipation.

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Overdosage

- No specific antidote available for overdose of alosetron hydrochloride.
- Patients should be managed with appropriate supportive therapy.

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Section 4:

How to Prescribe LOTRONEX®/alosetron hydrochloride

Please see complete Prescribing Information for LOTRONEX®/alosetron hydrochloride for full details about risks.

Dosage and Administration

- Usual Dose in Adults:
  - ✓ **To lower the risk of constipation, alosetron hydrochloride should be started at 0.5 mg twice-a-day.**
  - ✓ **Patients well controlled on 0.5 mg twice-a-day may be maintained on this regimen.**
  - ✓ **If, after 4 weeks, the 0.5 mg twice-a-day dosage is tolerated but does not adequately control IBS symptoms, increase dose to 1 mg twice-a-day, the dose used in controlled clinical trials.**
  - ✓ **Alosetron hydrochloride should be started at a dosage of 0.5 mg twice-a-day. Patients controlled on this dose may be maintained on this regimen.**
  - ✓ **If after 4 weeks, the 0.5 mg twice-a-day dosage is well tolerated but does not adequately control the IBS symptoms, then the dosage can be increased up to 1 mg twice-a-day.**

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Dosage and Administration (cont'd)

- Usual Dose in Adults (cont't):
  - ✓ **Alosetron hydrochloride should be discontinued in patients who have not had adequate control of IBS symptoms after 4 weeks of treatment with 1 mg twice-a-day.**
  - ✓ **Alosetron hydrochloride should be discontinued immediately in patients who develop constipation or signs of ischemic colitis.**
  - ✓ **Alosetron hydrochloride should not be restarted in patients who develop ischemic colitis.**
- Clinical trial and post-marketing experience suggest that debilitated patients or patients taking additional medications that decrease GI motility may be at greater risk of serious complications of constipation.
- Therefore, appropriate caution and follow-up should be exercised if alosetron hydrochloride is prescribed for these patients.
- Alosetron hydrochloride can be taken with or without food.

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Section 5:

LOTRONEX REMS Program™

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LOTRONEX REMS Program™

Prescriber Training

- Prescribers should read the full Prescribing Information (PI) and other training materials to understand the benefits and risks of treatment with LOTRONEX®/alosetron hydrochloride for severe diarrhea-predominant IBS.

- Prescribers can communicate the completion of training by filling out the Prescriber Completion of LOTRONEX REMS Program™ Training Form:
  - online at www.lotronexrems.com, or
  - via e-mail at contactclientservice@prometheuslabs.com, or
  - by fax to Prometheus Client Services at 1-877-816-4019.

The form must be completed and returned to Prometheus before a prescriber can be considered trained in the LOTRONEX REMS Program™.

LOTRONEX REMS Program™

- The REMS Training Kit includes the following:
  - REMS letter for Healthcare Providers
  - LOTRONEX REMS Program Prescriber Education Slide Deck
  - LOTRONEX REMS Program Safety Information Fact Sheet for Prescribers
  - LOTRONEX REMS Program Patient Education Sheet
  - Prescriber Completion of LOTRONEX REMS Program Training Form

LOTRONEX REMS Program™

Patient Education

- Once you have selected an appropriate patient for therapy:
  - ✓ provide the patient with the LOTRONEX® REMS Program Patient Education Sheet
  - ✓ review it together with the patient and explain the risks of therapy
  - ✓ answer any questions the patient may have.
- Instruct the patient to read the Medication Guide supplied with the product

LOTRONEX REMS Program™

Patient Responsibilities

Patients should be instructed to:

- read the LOTRONEX REMS Program Patient Education Sheet before starting LOTRONEX®/alosetron hydrochloride .
- read the Medication Guide before starting LOTRONEX®/alosetron hydrochloride and each time they refill their prescription.
- not take LOTRONEX®/alosetron hydrochloride if they are constipated.
- immediately discontinue LOTRONEX®/alosetron hydrochloride and contact their prescriber if they become constipated or have symptoms of ischemic colitis such as new or worsening abdominal pain, bloody diarrhea, or blood in the stool.
- immediately contact their prescriber again if their constipation does not resolve after discontinuation of LOTRONEX®/alosetron hydrochloride.
- resume LOTRONEX®/alosetron hydrochloride only if their constipation has resolved and after discussion with and the agreement of their treating prescriber.
- stop taking LOTRONEX®/alosetron hydrochloride and contact their prescriber if LOTRONEX®/alosetron hydrochloride does not adequately control IBS symptoms after 4 weeks of taking 1 mg twice-a-day.